REMARKS

Claims 1 and 6-8 are currently pending in the application. Applicant has added new claims 14-17, which are claims 1 and 6-8 with "L-arginine" deleted from the group of therapeutic compounds administered. Claims 1, 6-8, and 14-17 are in independent form.

The amendments to claims 1 and 6-8 of "identifying increased numbers of new neurons" have support on page 13, lines 16-18 ("Increased numbers of new neurons were identified when this compound was administered at and beyond 24 hours after onset of stroke.") Further support can be found on page 11, lines 21-28 ("Thus, neurons were identified by expression of NeuN, MAP2 and the astrocytes formed by GFAP. Measurements of neurogenesis were performed within specific regions of brian, the subventricular zone and the dentate gyrus. The data showed a significant increase in the numbers of BrdU positive cells in rats treated with DETANONO compared to those found in the untreated group."); page 17, lines 1-5 ("Rats treated with DETANONO have a significant increase in numbers of BrdU immunoreactive cells..."); page 21, line 26 – page 22, line 3 ("These data indicate administration of DETANONO to ischemic rats improves neurological functional recovery...administration of SNAP to ischemic rats also improves neurological functions.... These data, together with previous data showing that NO donor promotes neurogenesis, suggest that NO donor compounds enhance neurological functional recovery after stroke via promotion of neurogenesis in ischemic brain." – i.e. increased numbers of new neurons causes functional recovery); and page 25, lines 5-18 ("Administration of VIAGRA™ at doses of 2 or 5 mg/kg significantly increased TuJ1 immunoreactive cells...."). No new matter has been added.

Applicants expresses their gratitude for courtesies extended by the Examiner and her supervisor during a personal interview conducted with

Applicants' representative, Dr. Kenneth I. Kohn, that occurred December 11, 2007. During the personal interview, proposed amendments to the claims were discussed and it was suggested by the Examiner to file a Request for Continued Examination, including the proposed amendments.

Claims 1 and 6-8 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action holds that Applicant has not described with sufficient clarity what statins and phosphodiesterase inhibitors are contemplated and the claims encompass any statin or phosphodiesterase inhibitors known and unknown. No distinguishing features by members of those broad genera have been provided in the instant disclosure. In response thereto, Applicant submits herein a declaration stating that any statin or phosphodiesterase inhibitor can be used and are contemplated by the presently pending claims. References cited below can be found in the declaration.

More specifically, the declaration states that different phosphodiesterase 5 (PDE5) inhibitors have been tested [1, 7-9] as well as different statins [3, 5, 6]. Applicants employ PDE5 inhibitors, since PDE5 is an enzyme needed for hydrolysis of cGMP and Applicants objective is to increase cGMP to induce neurogenesis and recovery from neural injury. Applicants have successfully used the PDE5 inhibitor sildenafil with the methods of the present invention (p. 7, Example 3). Likewise, Applicants have performed many experiments using atorvastatin and simvastatin; two very different statins, one which passes through the blood brain barrier (simvastatin) and one which does not (atorvastatin). Both these agents show remarkable induction of neurogenesis and are highly effective in restoring neurological function after stroke, trauma and neural injury[3, 5, 6, 10]. The use of statins for the treatment of neural injury is also, in part based on the observations that statins induce cGMP. Thus, all PDE5 inhibitors as well as all statins increase cGMP, and the claims comply with the written description

requirement. Reconsideration of the rejection is respectfully requested.

Claim 1 stands rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,428,070 to Cooke, et al. Specifically, the Office Action holds that Cooke, et al. discloses administering L-arginine after vascular injury with emphasis on decreasing the effects of atherogenesis, and atherosclerotic vascular diseases such as stroke are higher in patients with non-insulin-dependent diabetes mellitus wherein the conditions may result in stroke. The Office Action holds that the drug L-arginine is administered after the injury (post) and cGMP is increased resulting in new neuron growth. Thus, the Office Action holds that one skilled in the art would have been motivated to administer L-arginine to patients post stroke in order to promote neurogenesis, or growth of new neurons, because L-arginine is the substrate for nitric oxide (NO) production and has been shown to induce an endothelium-dependent increase in cerebral blood flow in humans. Reconsideration of the rejection under 35 U.S.C. §103(a) as being unpatentable over the Cooke, et al. patent is respectfully requested.

The Cooke, et al. patent explicitly addresses the role of administering L-arginine as a substrate for nitric oxide (NO) in the treatment of atherosclerosis and restenosis. Although atherosclerosis is a minor risk factor for stroke, the reduction of atherosclerosis or restenosis of a coronary artery or even a cerebral artery (which is not the focus of the Cooke, et al. patent) has nothing to do with neurogenesis, brain plasticity, and inducing recovery from stroke as in the presently pending application.

The basic chemistry of the NO pathway dictates that cGMP is increased in response to NO. Therefore, administering a NO substrate will, based on the laws of chemistry, increase cGMP. In example 2 of the Cooke, et al. patent, column 9, line 22, the text reads, "the reduction in platelet aggregation was associated with a two-fold increase in cGMP content in

aggregated platelets from arginine treated animals". This is simple chemistry, that a substrate for NO will increase cGMP. There is, however, no statement or logical scientific connection that can be made relating cGMP to the induction of neurogenesis and recovery from stroke, as claimed by the presently pending independent claims. Nowhere in the Cooke, et al. patent, is there any statement or inference to the brain, to neurogenesis, to recovery from stroke and brain plasticity. Certainly Cooke, et al. does not disclose or suggest the presently added step to claim 1 of "identifying increased numbers of new neurons". One cannot infer in any way that a decrease in atherosclerosis and restenosis of a vessel is related to the production of new brain cells. The statements in the Cooke, et al. patent in column 3, lines 52-53 address the role of arginine and NO in restenosis, completely independent of neurogenesis, stroke, and recovery. This is a vascular issue about vessels that re-occlude and the rate of re-occlusion is reduced with these compounds. Likewise, the reference to col.9, lines 22-24, relates to the role of NO/L-arginine on aggregated platelets; again, not in anyway associated with the presently pending independent claims. The Cooke, et al. patent is directed towards a means to reduce vascular pathology, associated with atherosclerosis and re-occlusion of blood vessels. The presently pending claims are independent of vascular issues, and as discussed in the Declaration herein, Applicants have also shown that agents which increase cGMP such as PDE5 inhibitors and statins act directly on neurons and progenitor cells in brain to induce the production of new neural cells [1-8]. Applicants have also added claims 14-17 which do not recite "L-arginine", and Cooke, et al. does not disclose or suggest the other compounds recited in the claims for the methods of the present invention.

Since neither the cited reference alone or in combination with knowledge in the art suggests the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in

opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1, 6-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cooke, et al. patent taken with the Liao patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Cooke, et al. patent taken with the Liao, patent in view of the Kaposzta, et al. reference taken with the Ohtsuka, et al. reference is respectfully requested.

As stated above, the Cooke, et al. patent does not disclose or suggest the present invention because there is no disclosure or suggestion of neurogenesis or increased neural function with the administration of the compounds along with identifying increased numbers of new neurons as required by the presently pending independent claims. Further combining Cooke, et al. with the above cited references does not arrive at the present invention.

The Office Action has held that the Liao patent teaches a surprising connection was made in connection with the treatment of ischemic stroke, wherein brain injury reduction is measured by determining a reduction in the infarct size in treated versus control groups. At column 8, lines 62-65 there is further disclosed that the "brain injury reduction, as demonstrated in the examples below, can be measured by determining a reduction in infarct size in the treated versus the control groups." In other words, the treatment is similar to that of the Moskowitz patent previously cited in the present application, which does not provide the same results as accomplished by the method of the presently pending claims.

Contrary to the statement that "L-arginine is known for its properties of promoting neurogenesis (see Moskowitz, of record)" made by the Office Action, Applicants have previously stated that Moskowitz discloses no such thing and in fact makes the statement that neurons cannot regenerate. Applicants note that no cited prior art reference to date has shown regeneration of neurons or new neuron growth. This was commonly accepted knowledge in the art at the time of the present invention, which is why the results of the present invention are so unexpected. Therefore, *none of the cited prior art can perform the required steps of claims 1 and 6-8 of "identifying increased numbers of new neurons"*. Further with respect to the statement made by the Office Action, Applicant has included new claims 14-17 which do not recite the compound "L-arginine". Moskowitz does not disclose any evidence that L-arginine can be effective after an ischemic event, and Moskowitz does not disclose the other compounds recited by the claims even capable of being used to treat after an ischemic event.

As was found with regard to the Moskowitz patent, the Liao patent merely discloses that stroke can be treated during a finite period of time. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. The Liao patent discloses at column 9, lines 21-30 that the treatment can either be prophylactic or can be acute. The acute treatment is defined as "at the onset of symptoms of the condition or at the onset of a substantial change in the symptoms of an existing condition." This definition is commensurate in scope with the knowledge of those of skill in the art defined above. Essentially, the Liao patent discloses treatment before or during the stroke itself in order to afford protection from stroke.

While Liao states that "the invention ... is useful for treating subjects with hypoxia-induced conditions", there is no reason to interpret this

statement to mean that treatment is given after stroke as it must be read in the context of the whole patent disclosure (col. 3, lines 45-46). While conditions caused by hypoxia can be treated, this treatment is given prior to any hypoxia-induced event. There is no indication from the Liao patent that treatment can be given post ischemic event. Every example given by Liao is directed to prophylactic treatment before ischemia occurs, especially in Example 17 (simvastatin treatment for 14 days followed by production of cerebral ischemia). Furthermore, nowhere in the Liao patent is there any statement or inference to neurogenesis (i.e. the generation of new neurons), recovery from stroke with treatment after such stroke has happened, or recovery of brain plasticity as required by the presently pending independent claims.

Applicants previously presented a journal article by Liao (proc. Natl. Sci. USA, Vol. 95, pp. 8880-8885, July 1998) to further provide evidence that Liao only discloses prophylactic treatment or at most treatment during a stroke. This article also examines the effect of HMG-CoA reductase inhibiting drugs on ischemia through their mechanism of up-regulating endothelial nitric oxide synthase. The goal of the article is "to determine whether statin administration confers protection against ischemic stroke" and therefore simvastatin was administered daily for 14 days to mice before MCA occlusion (p. 8881). Further, the authors state that "the major finding in this study is that prophylactic treatment with HMG-CoA reductase inhibitors protects against ischemic strokes after focal brain ischemia" (p. 8884). This article teaches much of the same methods and findings with simvastatin as the Liao patent. Accordingly, there is no motivation for treatment after the stroke is complete, i.e. post ischemic event, since this is a point in time substantially after the onset of the symptoms.

Finally, with regard to the Kaposta, et al. and Ohtsuka, et al. references, these references merely disclose use of compounds

prophylactically. There is no disclosure for the use of the compounds post ischemic event for creating neurogenesis. Since none of the cited references alone or in combination with one another suggest the currently claimed invention, it is respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

Claims 1 and 6-8 of this application have further been rejected as unpatentable based on provisional non-statutory obviousness-type double patenting over co-pending Application No. 10/500,694. These rejections can be readily overcome by the filing of a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) or (d). Applicant stands ready to provide the appropriate terminal disclaimer upon the indication of the allowance of the pending claims.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In conclusion, it is respectfully submitted that the presently pending claims are in condition for allowance, which allowance is respectfully requested. Applicant respectfully requests to be contacted by telephone if any remaining issues exist.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: December 17, 2007

CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

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I hereby certify that this correspondence is being electronically filed with the United States Patent & trademark Office on the above date.

Connie Herty

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chopp, et al.

Serial No. 10/075,715 Group Art Unit: 1614

Filed: 02/13/2002 Examiner: GEMBEH, Shirley V.

For: NITRIC OXIDE DONORS FOR INDUCING NEUROGENESIS

Attorney Docket No. 1059.00073

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

I, Dr. Michael Chopp, being duly sworn, do hereby state that:

1. I am a co-inventor of the above-captioned application.

2. I am skilled in the art and have worked extensively in the field of neurogenesis.

3. Relating to the issue of specifying phosphodiesterases (PDE) 5 and statins in the presently pending patent application, different phosphodiesterase 5 inhibitors have been tested [1, 7-9] as well as different statins [3, 5, 6]. We obviously employ PDE5 inhibitors, since PDE5 is the enzyme needed for hydrolysis of cGMP and our objective is to increase cGMP to induce neurogenesis and recovery from neural injury. We have successfully used the PDE5 inhibitor sildenafil with the methods of the present invention (p. 7, Example 3). Likewise, we have performed many experiments using atorvastatin and simvastatin; two very different statins, one which passes through the blood brain barrier (simvastatin) and one which does not (atorvastatin). Both these agents show remarkable induction of neurogenesis and are highly effective in restoring neurological function after stroke, trauma and neural injury[3, 5, 6, 10]. The use of statins for the treatment of neural injury is also, in part based on the observations that statins induce cGMP. Thus, all PDE5 inhibitors as well as all statins increase cGMP, and the claims comply with the written description requirement.

1. Zhang R, Wang Y, Zhang L, Zhang Z, Tsang W, Lu M, Chopp M. Sildenafil (viagra) induces neurogenesis and promotes functional recovery after stroke in rats. *Stroke*. 2002;33:2675-2680.
2. Wang L, Gang Zhang Z, Lan Zhang R, Chopp M. Activation of the pi3-k/akt pathway mediates cgmp enhanced-neurogenesis in the adult progenitor cells derived from the subventricular zone. *J Cereb Blood Flow Metab*. 2005;25:1150-1158
3. Chen J, Zhang ZG, Li Y, Wang Y, Wang L, Jiang H, Zhang C, Lu M, Katakowski M, Feldkamp CS, Chopp M. Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. *Ann Neurol*. 2003;53:743-751
4. Chen J, Zhang C, Jiang H, Li Y, Zhang L, Robin A, Katakowski M, Lu M, Chopp M. Atorvastatin induction of vegf and bdnf promotes brain plasticity after stroke in mice. *J Cereb Blood Flow Metab*. 2005;25:281-290
5. Chen J, Zacharek A, Li A, Zhang C, Ding J, Roberts C, Lu M, Kapke A, Chopp M. Vascular endothelial growth factor mediates atorvastatin-induced mammalian achaete-scute homologue-1 gene expression and neuronal differentiation after stroke in retired breeder rats. *Neuroscience*. 2006;141:737-744
6. Lu D, Qu C, Goussev A, Jiang H, Lu C, Schallert T, Mahmood A, Chen J, Li Y, Chopp M. Statins increase neurogenesis in the dentate gyrus, reduce delayed neuronal death in the hippocampal ca3 region, and improve spatial learning in rat after traumatic brain injury. *J Neurotrauma*. 2007;24:1132-1146
7. Zhang L, Zhang RL, Wang Y, Zhang C, Zhang ZG, Meng H, Chopp M. Functional recovery in aged and young rats after embolic stroke: Treatment with a phosphodiesterase type 5 inhibitor. *Stroke*. 2005;36:847-852
8. Zhang RL, Zhang Z, Zhang L, Wang Y, Zhang C, Chopp M. Delayed treatment with sildenafil enhances neurogenesis and improves functional recovery in aged rats after focal cerebral ischemia. *J Neurosci Res*. 2006;83:1213-1219
9. Zhang L, Zhang Z, Zhang RL, Cui Y, Lapointe MC, Silver B, Chopp M. Tadalafil, a long-acting type 5 phosphodiesterase isoenzyme inhibitor, improves neurological functional recovery in a rat model of embolic stroke. *Brain Res*. 2006
10. Seyfried D, Han Y, Lu D, Chen J, Bydon A, Chopp M. Improvement in neurological outcome after administration of atorvastatin following experimental intracerebral hemorrhage in rats. *J Neurosurg*. 2004;101:104-107

The undersigned declares further all statements made herein of his knowledge are true and that all statements made upon information and belief are believed to be true, and further that the statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12/5, 2007

Dr. Michael Chopp